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IMMUNOHISTOCHEMICAL EXPRESSION OF PROSTATE SPECIFIC ANTIGEN (PSA) IN BENIGN AND MALIGNANT BREAST LESIONS

Pathology

Dr Sumiti Gupta Professor, Deptt of Pathology, Pt BD Sharma, PGIMS, Rohtak.

Dr Priyanka Rawat Junior Resident, Deptt of Pathology, Pt BD Sharma, PGIMS, Rohtak.

Dr Nishtha Gupta Exhousesurgeon, Deptt of anaesthesiology, Pt BD Sharma, PGIMS, Rohtak.

Dr Pooja Rathee* Junior Resident, Deptt of Pathology, Pt BD Sharma, PGIMS, Rohtak. *Corresponding Author

Dr Nisha Marwah Professor, Deptt of Pathology,Pt BD Sharma, PGIMS, Rohtak.

Dr Meenu Gill Professor, Deptt of Pathology,Pt BD Sharma, PGIMS, Rohtak.

Dr Sunita Singh Senior Professor and Head of Department, Deptt of Pathology, Pt BD Sharma, PGIMS, Rohtak.

ABSTRACT

Immunohistochemical expression of prostate specific antigen (PSA) is an aid in determining the prostatic origin of the malignant cells. However, PSA in small amounts have also been found in non-prostatic tissues and tumors, for example in some breast carcinomas as well as benign breast lesions. Our aim was to evaluate the prevalence and value of immunohistochemical expression of PSA in both benign and malignant breast lesions. Sections of formalin fixed, paraffin embedded tissue samples from 30 benign and 30 malignant breast lesions were immunostained for PSA along with routine estrogen receptor (ER), progesterone receptor (PR) and Her2/neu. Stained sections were reported according to the intensity of staining and percentage of cells showing PSA staining. The relationship of PSA expression and other markers, age, lymph node status, histological grade, and tumor subtype was studied. PSA were expressed in 9/30 (30%) benign cases and in 17/30 (56.7%) of malignant cases. 64.7% (11/13) of PSA positive cases were ER positive and 58.8% (10/13) were PR positive. We found an inverse correlation between HER2/neu and PSA (p=0.05). Although most of the PSA-positive carcinomas were lymph node-negative, well and moderately differentiated, we did not find any statistically significant correlations with PSA expression. Among the benign cases, we found a correlation between size and the PSA positivity (p value 0.025) only.

KEYWORDS

Prostate Specific Antigen, Estrogen Receptor, Progesterone Receptor, Invasive breast carcinoma, Immunohistochemistry.

INTRODUCTION

The prevalence of benign breast diseases is 68% among all breast diseases and 6.9% among all diseases of women. Most of the lesions found in breast are benign. Benign breast lesions may present with great range of symptoms or may be found incidentally. The incidence of benign lesions rises during 2nd and 3rd decade of life whereas malignant lesions are more common in menopausal women.[1]

Benign lesions are far more common than malignant ones.[2] Breast cancer is one of the most common malignancies and cause of cancer death among women worldwide. It is estimated that about 508,000 women died in 2011 worldwide due to breast cancer (Global Health Estimates, WHO 2013). In 2012, in India, there were 144,937 new cases of carcinoma breast out of which 70,218 women died of breast cancer suggesting that every 2nd woman, newly diagnosed with breast cancer, is dying of it.[3]

It has an important role in the pathology of breast, as well as other benign tumors or malignant tumors. There is a growing list of available antibodies. The most common IHC markers for breast include: Cytokeratin, Estrogen, Progesterone, GATA 3, Mammaglobin, HER2/neu, E cadherin, Ki 67 index, EGFR 2 and p53.[4]

Prostate specific antigen (PSA) is a glycoprotein initially isolated in 1979 and one of three human kallikrein gene products (hk1, hk2, and hk3). PSA or kallikrein 3 (KLK3) is a 33 kDa serine protease found at high concentrations in seminal plasma and prostate epithelial cells and at low concentrations in healthy male serums.[5]

It was postulated that appearance of PSA in breast tumors is due to PSA derepression by steroid hormone receptors bound to either estrogens, progestins or androgens. PSA might facilitate cancer cell migration and invasion by digesting the basement membrane, extracellular matrix and connective tissue.[6]

PSA was detected in 33% of normal breast tissue, 65% of benign tumor and 28% of malignant tumors[7].

MATERIALS AND METHODS

In this study, available formalin fixed and paraffin embedded tissue samples of 30 benign and 30 malignant breast lesions from Department of Pathology, PT B D Sharma PGIMS, Rohtak, Haryana, India were evaluated. The sections were stained for PSA in addition to routine ER, PR Her2/neu for the carcinoma cases. Brown granular, focal or diffuse cytoplasmic staining was taken as positive for PSA. Human prostate epithelium was used as control (Score - 4 very strong immuno reaction).The intensity of positive immunostaining in the cytoplasm of tumor cells was graded into 3 categories. Histoscore was calculated by multiplying fraction of stained cell with intensity of staining.[8]

HISTOSCORE		INTENSITY
0-0.04	0	Negative
0.05-0.75	+1	Weak
0.73-1.4	+2	Moderate
1.5-3	+3	Strong

PSA expression was then correlated with the various clinico pathological parameters such as the age of the patient, the type and size of lesion, lymph node involvement, MBR grade, NPI score, and ER, PR and HER2/neu expression. Chi square test was used to assess the association and a value of $p<0.05$ was taken as significant.

RESULT:

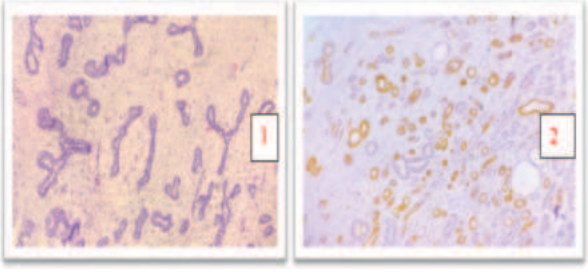
Table1: Observations made for benign breast lesions.

	Categories	N	PSA		Chi square	P value
			Negative (N (%))	Positive (N (%))		
AGE	<=45 year	29	21 (100)	8 (88.9)	2.414	0.12
	>45 year	1	0 (0)	1 (11.1)		
MENOPAUSAL STATUS	Attained	6	4 (19)	2 (22.2)	0.04	0.842
	Not Attained	24	17 (81)	7 (77.8)		
Size	<2 cm	2	0 (0)	2 (22.2)	5	0.025
	>=2 cm	28	21 (100)	7 (77.8)		
HISTOLOGICAL TYPE	ADENOSIS	1	1 (4.8)	0 (0)	4.603	0.466
	FIBROADENOMA	24	16 (76.2)	8 (88.9)		

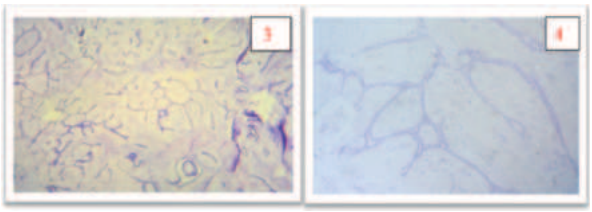
	FIBROADENOMA WITH APOCRINE METAPLASIA	1	0 (0)	1 (11.1)		
	GYNECOMASTIA	2	2 (9.5)	0 (0)		
	INFLAMMATORY LESION	1	1 (4.8)	0 (0)		
	PHYLLOIDES TUMOR	1	1 (4.8)	0 (0)		

Table2: Correlation of PSA expression with different clinico pathological parameters showed following result.

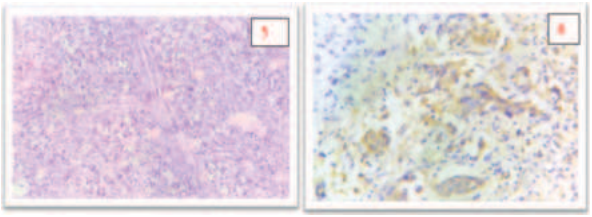
	Categories	N	PSA		Chi square	P value
			Negative (N (%))	Positive (N (%))		
HISTOLOGICAL TYPE	IDC, NOS	29	12 (92.3)	17 (100)	1.353	0.245
	METAPLASTIC CARCINOMA	1	1 (7.7)	0 (0)		
HISTOLOGICAL GRADE	METAPLASTIC CARCINOMA	1	1 (7.7)	0 (0)	1.969	0.579
	I	11	5 (38.5)	6 (35.3)		
	II	11	5 (38.5)	6 (35.3)		
	III	7	2 (15.4)	5 (29.4)		
ER SCORE	0	15	11 (84.6)	4 (23.5)	12.624	0.049
	1	2	0 (0)	2 (11.8)		
	3	1	0 (0)	1 (5.9)		
	4	3	0 (0)	3 (17.6)		
	5	2	1 (7.7)	1 (5.9)		
	6	6	1 (7.7)	5 (29.4)		
	7	1	0 (0)	1 (5.9)		
ER +/-	Negative	17	11 (84.6)	6 (35.3)	7.298	0.007
	Positive	13	2 (15.4)	11 (64.7)		
PR SCORE	0	10	9 (69.2)	1 (5.9)	16.833	0.019
	1	2	0 (0)	2 (11.8)		
	2	3	1 (7.7)	2 (11.8)		
	3	2	0 (0)	2 (11.8)		
	4	6	0 (0)	6 (35.3)		
	5	2	1 (7.7)	1 (5.9)		
	6	2	1 (7.7)	1 (5.9)		
	7	3	1 (7.7)	2 (11.8)		
PR +/-	Negative	17	10 (76.9)	7 (41.2)	3.833	0.049
	Positive	13	3 (23.1)	10 (58.8)		
HER2/NEU INTENSITY	0	7	2 (15.4)	5 (29.4)	2.754	0.431
	1	7	2 (15.4)	5 (29.4)		
	2	10	5 (38.5)	5 (29.4)		
	3	6	4 (30.8)	2 (11.8)		
HER2/NEU +/-	Negative	15	5 (38.5)	10 (58.8)	1.222	0.269
	Positive	15	8 (61.5)	7 (41.2)		
ER AND PR	Negative	10	9 (90)	1 (10)	11.825	0.001
	Positive	9	1 (11.1)	8 (88.9)		
LYMPH NODE STATUS	Negative	13	6 (46.2)	7 (53.8)	0.074	0.785
	Positive	17	7 (41.2)	10 (58.80		



Photomicrograph Showing Fibroadenoma With Positive Psa Expression Fig 1: (H&E, 100X) Fig 2: PSA Positive, Strong Intensity (IHC 100X)



Photomicrograph Showing Gynecomastia With Negative Psa Expression Fig 3: H & E, 100X Fig 4: PSA Negative, IHC 100X



Photomicrographs Showing Idc (nos Type) Mbr Grade Iii FIG 5: H & E, 200X, Fig 6: PSA Positive (IHC, 200X)

DISCUSSION

PSA expression and PSA serum levels can be used as a prognostic indicator for breast carcinoma cases as observed in various studies. It was also observed that PSA expression is associated with higher age group, well differentiated low grade tumors. Several studies had found a direct relationship between ER and PR expression and PSA immunoreactivity and an inverse relationship with HER2/Neu expression.

Table3: Comparison Of Distribution Of Benign And Malignant Cases With Other Studies

Various Studies	Number of cases examined	PSA POSITIVE CASES	P value
Yu et el9 (n= 274)	48- benign 199 malignant 36 normal	17 (35.4%) 56 (28.1%) 12 (33.3%)	BBD and CA <0.001 (S) N and CA 0.529 (NS) BBD and N 0.008 (S)
Bee Hoon et al10 (n= 43)	23 benign 20 malignant	10 (43.5%) 8 (40%)	1.00 (NS)
Kraus et al11 (n= 91)	5 benign 86 malignant	0 (0%) 3 (3.5%)	1.00 (NS)
OUR STUDY	30 benign 30 malignant	9(30%) 17 (56.7%)	0.037 (S)

Out of 30 benign cases, PSA positivity was only in 9 (30%) cases whereas other 21 cases were negative for PSA. However, intensity of PSA expression was more in benign cases compared to malignant cases. Our study was in concordance to studies of Yu He et al[9] and Bee Hoon et al[10]. In our study we found that PSA expression was associated more with the size more than 2 cm (p value 0.025).

The present study constituted a total of 60 cases from the patients with the age ranging from 10 – 75 years. The mean age in our study for benign cases is 50.2 years. However, we did not find any statistical correlation (p value 0.12) between age of the patient and PSA expression as was observed by Yu He et al[9], Bee Hoon et al[10] and Kraus et al[11].

In benign breast conditions our study demonstrated PSA positivity in pre-menopausal and reproductive age group whereas no expression was found for postmenopausal cases. There was no statistical significance between the two groups (p value 0.842). Our study is in concordance with the study of Bee Hoon et al[10] (p value 1.00).

30 cases of benign conditions included fibroadenoma, apocrine metaplasia, inflammatory lesion, gynecomastia and phylloides tumor. In many studies, including Yu He et al[9], Bee Hoon et al[10] more number of fibroadenoma cases showed PSA positivity compared to other benign lesions. Similar findings were observed in our study also.

Table4: Comparison Of Distribution Of Malignant Cases With Psa Positivity With Other Studies

VARIUS STUDIES	NO OF CASES	PSA POSITIVE
Diamendis et al6	474	90 (19%)
Yu et al9	199	56 (28.1%)
Kidwai et al12	26	6 (23%)
Narita et al13 2006	53	32 (60.3%)
OUR STUDY	30	17(56.7%)

In our study, malignant cases (56.7%) showed PSA expression of weak to moderate intensity (1+ and 2+). Our study is in concordance with several other studies mentioned in Table 38 like Narita et al.[13]

Table5: Comparison Of Various Studies On The Basis Of Er Pr Status With Present Study

VARIOUS STUDIES	ER+/ER-	PSA +	P VALUE	PR+/PR -	PSA +	P VALUE
Diamendis et al6	393 / 132	127 / 24	0.002 (S)	321 / 204	111/40	<0.001 (S)
Black et al14	263/ 73		<0.001 (S)	262 / 74		<0.001 (S)
Ilvan et al15	63/46	11/0	0.002(S)	61/48	11/0	0.002(S)
Narita et al13 2006	20/33	14/18	0.2648	22/31	16/16	0.1215
Narita et al16 2008	105/131	51/54	0.26	118/118	62/43	0.01 (S)
Mohammadizadeh et al17	NA	NA	0.015 (S)	NA	NA	0.8
OUR STUDY	13/17	11/6	0.007 (S)	15/14	12/5	0.050 (S)

Statistical significance (p value 0.007) was found between PSA expression and ER expression in our study which is in accordance with studies of Diamendis et al[6], Black e al[14], Ilvan et al[15] and Mohammadizadeh et al[17] but our study is in discordance with study done by Narita et al[13] in which they concluded that ER/PR expression did not show any significant correlation with PSA immunoreactivity.

Also a statistical significance was noted between PR score (p value 0.019) and PSA expression. Our study is in concordance with studies of Diamendis et al[6], Black e al[14], Ilvan et al[15] and not in concordance with Mohammadizadeh et al[17] and Narita et al[13] as shown in Table 42.

We also found a statistical correlation (p value 0.001) between combined ER and PR status with the PSA expression.

In our study, we observed an inverse relationship between HER2/Neu and PSA which is similar to studies done by Narita et al[13,16], Bee Hoon et al[10] as shown in Table 43 but did not find any statistical correlation (p value 0.269) between PSA expression and Her2/neu expression.

Table 6: Showing Comparison Of Various Studies On The Basis Of Her2/neu Status With Present Study

Various studies	HER2/neu +/-	PSA +	P VALUE
Narita et al40 2006	13/40	6/27	0.0339 (S)
Bee Hoon et al51	9/11	5/3	>0.05
Narita et al 522008	72/138	23/70	0.006 (S)
OUR STUDY	16/14	7/14	0.269

When PSA positive and negative groups were taken into consideration, no statistically significant difference was found between PSA expression and age of the patient, menopausal status, tumor size, lymph node status, histological type, MBR grade and NPI score. We observed that PSA was more positive in patients > 50 years of age. We analysed the immunoreactivity of the PSA with tumor stage and grade and it was observed that PSA positive tumors are associated with earlier disease stage and grade but this did not reach statistical significance as the number of samples per group were relatively small.

CONCLUSION

From this study it was concluded that PSA is present in both benign and malignant lesions of the breast. In our study, PSA immunoreactivity was seen in 56.7% of malignant lesions and 30% of benign lesions. Although from this study we could not evaluate the prognostic value of PSA in breast malignancies. PSA was significantly associated with some pathological parameters that are known to be associated with better prognosis like early stage, well and moderately differentiated tumors, ER/PR positive and Her2/neu negative breast carcinomas. Since the data from patient's outcome was not available in our study, we could not comment on relationship of PSA expression and patient's prognosis. However, further studies should undertake to investigate the correlation between PSA expression and the clinical behaviour, particularly the prognosis and treatment response of breast cancers.

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